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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/419,328	10/15/99	ROOK A	PENN-0701

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EXAMINER	
JIANG, D	
ART UNIT	**PAPER NUMBER**
1646	10

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/419,328	Applicant(s) ROOK, ALAIN H.	
	Examiner Dong Jiang	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED OFFICE ACTION

Applicant's amendment in paper No. 9, filed on 06 August 2001 is acknowledged and entered. Following the amendment, claim 2 is canceled, claim 3 is amended, and the new claim 4 is added. Currently claims 1, 3 and 4 are pending and under consideration.

Withdrawal of Objections and Rejections:

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (Ann NY Acad, 1996, 795:310-318), in view of Verbik et al. (Clin Exp Metastasis, 1996, 14:219-229) is moot as the applicant has canceled the claim.

The rejection of claim 3 under 35 U.S.C. 102(a) as being anticipated by Lee et al. (Leukemia and Lymphoma, 1998 May, 29(5-6):427-38) is withdrawn in view of applicant's amendments.

The rejection of claim 3 under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996), and further in view of Osaki et al. (J. Immunol., 1998 February, 160: 1742-49) is withdrawn in view of applicant's argument.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Rook et al. (Clin Exp Immunol, 1997 January, 107 Suppl 1: 16-20) for the reasons cited in the last Office Action, paper No. 7, mailed on 14 March 2001, at page 2.

Applicant's arguments and declaration, filed on 6 August 2001 (paper No. 9) have been fully considered, but is not deemed persuasive for reasons below:

At page 4 of the response, the applicant argues that Rook does not teach treatment in humans, it was not until after the publication at issue that the clinical efficacy of IL-12 in CTCL

patients was disclosed, and presents a declaration by the inventor. The declaration filed under 37 CFR 1.131 has been considered but is ineffective to overcome the prior art reference by Rook. The evidence submitted is insufficient to establish a reduction to practice of the invention prior to the effective date of the prior art reference. It is noted that the declaration fails to provide any *evidence* that the clinical efficacy of IL-12 was disclosed only after the publication, and it is merely an allegation of such. Therefore, the declaration is insufficient to overcome the reference, in which Rook teaches IL-12 treatment in humans. Furthermore, *even if* the declaration had provided sufficient evidence, Rook's reference at least clearly suggests the clinical application of IL-12 to treat human CTCL as stated that "these studies led to a phase I trial of IL-12 to treat CTCL" (the abstract), and clearly provides a reasonable expectation of success because such clinical trial must have been approved by FDA. Thus, a rejection under 35 U.S.C. 103(a) as being unpatentable over the same reference would apply.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (Ann NY Acad, 1996, 795:310-318), in view of Verbik et al. (Clin Exp Metastasis, 1996, 14:219-229) for the reasons cited in the last Office Action, paper No. 7, mailed on 14 March 2001, at pages 3-6.

Applicants argument has been fully considered, but is not deemed persuasive for reasons below:

At page 6 of the response, the applicant argues that the cited combination of prior art references fails to meet all of the criteria to establish a prima facie case of obviousness under 35 U.S.C. 103(a). The applicant further argues that neither of the cited references provides one of skilled in the art with a reasonable expectation of successfully treating CTCL in a human via administering IL-12 alone or in combination with an IFN-γ stimulating agent, and Rook does not

teach a method for in vivo treatment (page 7, paragraphs 2-3). This argument is not persuasive because the requirement for a reasonable expectation of success does not rest on a complete certainty of success. Virtually all initial clinical applications are based on in vitro and/or in vivo animal studies, and it is impossible for a pre-clinical trial reference to teach and to ensure the absolute certainty of success in treating human diseases before a human clinical trial. Therefore, a prior art reference only needs to provide an indication of a *reasonable expectation* of success, and the cited combination of prior art references has provided such, as cited in the last Office Action. In particular, the teachings by Verbik that by day 16 all control mice had died of massive tumor burden in their liver and lungs, no tumor nodules were present in the IL-12 treated mice 60 days post tumor inoculation clearly demonstrate in vivo antitumor properties of IL-12 (page 223, the left column).

Further, At page 8 of the response, applicant argues that cytokine pathways are extremely complex, and success of administration of a single cytokine to a patient of CTCL can not reasonably be predicted based upon Rook's in vitro experiments, and Verbik's teaching of unexplained early death of IL-12 treated animals, and possibly because of GI damage caused by IFN-γ, which is induced by IL-12 would not motivate to administer IL-12 to a human with any expectation of success, on the contrary, a skilled person would refrain from such application (the second and the third paragraphs).

The Examiner would like, first, to point out a misquotation of Verbik's reference by the applicant. At pages 7-10, and 12 of the response, applicant repetitively indicates that Verbik teaches, on page 227 of the reference, unexplained early death of IL-12 treated animals. Contrary to applicant's statement, Verbik teaches that the *combination* of IL-12 *and* IL-2-ASC resulted in early deaths for some of the mice when compared to the mice receiving IL-2-ASC alone or IL-12 alone (page 227, lines 1-7 of the right column), and Verbik teaches clearly that IL-12 alone exhibits strong in vivo antitumor effect (Figures 1 and 2, and page 223, lines 13-15 of the left column), and no early death for IL-12 treated mice comparing to mice in the control group, in which all animals died by day 16, as clearly demonstrated in Figure 1, thus Verbik's teaching provides an indication for a *reasonable expectation* of success of IL-12 treatment for the human disease. Even if such adverse effect were indicated, a reasonable expectation of success is based on the overall positive effect and in view of any negative side effect or adverse

effect. Almost all compositions for treatment have some negative effects, especially those for cancer therapy. It is well known that most cancer therapy medications target rapid proliferating cells including both tumor cells and healthy cells such as gastrointestinal (GI) cells, and GI adverse effect is, therefore, common for these medications, and is not used as a sole indication to cease the clinical application.

Therefore, the combined references clearly suggest the motivation for treatment of lymphoma with IL-12, and all of the claim limitations of claim 1, and provide an indication of a reasonable expectation of success for the reasons set forth above and in the previous Office Action.

With respect to claim 3, applicant presents the same arguments as above at page 9, the complexity of the cytokine pathways, and Verbik's teachings of adverse effect of IL-12, which is, as the Examiner points out above, a misquotation of the reference. Applicants argument has been fully considered, but is not deemed persuasive for the same reasons above.

Claim 3 remains further rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996) and Verbik et al. as applied to claims 1 and 3 above, and further in view of Rook et al. (1997) for the reasons cited in the last Office Action, paper No. 7, at pages 5 and 6.

Applicants argument has been fully considered, but is not deemed persuasive for reasons below:

At page 12 of the response, the applicant argues that Rook (1997) does not teach administration of IL-12 or IL-12 with any other component *to a human*, and while significant suppression of growth of malignant CD4+ cells by IL-12 and IFN-α was suggested in vitro, there is no indication that this combination would be successful in humans (the second paragraph). This argument is not accurate because Rook clearly teaches that "these studies (all in vitro) led to a phase I trial of IL-12 to treat CTCL" (the abstract), which is administration of IL-12 *to a human*. Further, Rook's statement also indicates FDA approval of IL-12 therapy in human, which is based on Rook's *in vitro* experiment results, and suggest a reasonable expectation of success in human application. Additionally, as addressed above, all initial clinical applications have to depend upon in vitro and/or in vivo animal studies. Although Rook does not teach administration of IL-12 with any other component *to a human*, the reference clearly

demonstrates the suppressive effect of IL-12 plus IFN-α on the growth of malignant CD4+ cells in vitro. In the absence of negative evidence, Rook's in vitro results indicate more likely than not that such combination treatment would be beneficial for the human disease, and provide an indication of a reasonable expectation of success when applied in a human.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (Ann NY Acad, 1996, 795:310-318).

Teachings by Rook's reference are summarized in the previous Office Action, paper number 7, at pages 2-4, and above.

Although Rook does not teach a method for in vivo treatment, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method as claimed for treatment of advanced CTCL in a human by administering recombinant IL-12 *with* an adjunct therapeutic agent stimulating IFN-γ production, based upon the strong teachings from Rook's in vitro studies and suggestions, that SzS, an advanced form of CTCL, is characterized with a marked depressed IFN-γ production, and a marked defect in IL-12 production by PBMCs, and that the presence of normal *in vivo* concentrations of *both* IL-12 and IFN-γ could favor the enhancement of anti-tumor cell-medicated immune responses that are deficient in this disorder. One of ordinary skill in the art would have been motivated to treat human CTCL by administering recombinant IL-12 *with* an adjunct therapeutic agent stimulating IFN-γ production at Rook's suggestion and reasonably would have expected success because such combination would correct both defects of IL-12 and IFN-γ in these patients, thus enhance anti-tumor immune responses.

Although Rook's reference is silent about "a pharmaceutically acceptable carrier" with IL-12 in above method, it is well known in the art that a purified protein agent is usually used in combination with other agent(s) (such as dissolving solutions), and can not be used as its crystal form alone. The fact that recombinant IL-12 is used in media in Rook's method indicates the protein is dissolved. Dissolving solutions, such as water, buffers, or media, meet the limitation of being "a pharmaceutically acceptable carrier".

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

DJ
10/12/01